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Comparison of treatment regimens for cytomegalovirus retinitis in patients with AIDS in the era of highly active antiretroviral therapy

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Abstract

Purpose—To describe the outcomes of different treatment approaches for cytomegalovirus (CMV) retinitis in the era of highly active antiretroviral therapy (HAART).

Design—Prospective cohort study, the Longitudinal Study of the Ocular Complications of AIDS.

Participants—250 patients with CMV retinitis and CD4+ T cells <100 cells/μL (n=221) at enrollment or incident retinitis (n=29) during cohort follow-up.

Methods—The effects of systemic therapy (vs. intraocular therapy only) on systemic outcomes and the effect of intraocular therapies (ganciclovir implants, intravitreal injections) on ocular outcomes were evaluated.

Main Outcome Measures—Mortality, CMV dissemination, retinitis progression, treatment side effects.

Results—Regimens containing systemic anti-CMV therapy were associated with a 50% reduction in mortality (adjusted hazard ratio [HR]=0.5; 95% confidence interval [CI] = 0.3, 0.7; P=0.006), 90% reduction in new visceral CMV disease (adjusted HR=0.1; 95% CI = 0.04, 0.4; P=0.004), and among those with unilateral CMV retinitis at presentation, an 80% reduction in

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This article contains additional online-only material. The following should appear online-only: Table 1 and the Research Group

second eye disease (adjusted HR=0.2; 95% CI= 0.1, 0.5; P=0.0005) when compared to those using only intraocular therapy (implants or injections). Compared to systemic treatment only, regimens containing intravitreal injections had greater rates of retinitis progression (adjusted HR=3.4, P=0.004) and greater visual field loss (for loss of ½ of the normal field, adjusted HR=5.5, P<0.01). Intravitreal implants were not significantly better than systemic therapy (adjusted HR for progression =0.5, P=0.26, and for loss ½ visual field =0.5, P=0.45), but the sample size was small. Hematologic and renal side effect rates were similar between those groups with and without systemic anti-CMV therapy. The rate of endophthalmitis among those treated with intravitreal injections was 0.017/EY (95% CI =0.006, 0.05) and among those treated with an implant 0.01/EY (95% CI =0.002, 0.04).

Conclusions—In the HAART era, systemic anti-CMV therapy, while there is immune compromise, appears to provide benefits in terms of longer survival and decreased CMV dissemination.

Cytomegalovirus (CMV) retinitis is the most common ocular opportunistic infection in patients with the Acquired Immune Deficiency Syndrome (AIDS).¹⁻³ It is a late stage infection, occurring primarily among those with CD4+ T cells < 50 cells/μL.⁴⁻⁷ The introduction of highly active antiretroviral therapy (HAART) resulted in an 80–90% reduction in the incidence of CMV retinitis, but new cases continue to occur.⁷⁻¹¹ Furthermore, patients with CMV retinitis begun on HAART may experience immune recovery sufficient to control the retinitis without anti-CMV therapy.¹²⁻¹⁸ The Department of Health and Human Services (DHHS) guidelines for the management of opportunistic infections in patients with AIDS recommends discontinuing anti-CMV therapy if the CD4+ T cells have increased to a level above 100 cells/μL for 3 to 6 months.^{17,18} However, even among those patients with newly-diagnosed CMV retinitis in the HAART era who are HAART-naïve and can expect immune recovery, treatment for at least 6 months is recommended to prevent the complications of CMV retinitis.^{3,19}

Treatments for CMV retinitis include intravenous ganciclovir (Cytovene, Roche Pharmaceuticals, [Nutley, NJ, USA]) the oral pro-drug valganciclovir (Valcyte, Roche Pharmaceuticals), intravenous foscarnet (Foscavir, Astra Zeneca Pharmaceuticals LP, [Wilmington, DE, USA]), intravenous cidofovir (Vistide, Gilead [Foster City, CA, USA]), intravitreal injections of ganciclovir or foscarnet, and the ganciclovir implant (Bausch and Lomb Pharmaceuticals Inc., [Tampa, FL, USA]). The efficacy of these treatments has been demonstrated in randomized clinical trials, and several comparative trials have been performed, largely in the pre-HAART era.³ Results from these trials demonstrated that regimens containing the ganciclovir implant controlled the retinitis better than those giving systemic ganciclovir alone, and regimens containing systemic therapy prevented dissemination (second eye involvement in a patient with unilateral disease and new onset visceral disease) better than those with intraocular therapy alone.^{3,20,21} Furthermore, data from cohort studies demonstrated improved survival with systemic therapy for CMV.²² However, because these studies largely were conducted in the pre-HAART era, because fewer data are available on the outcomes of different treatment regimens in the HAART era, and because HAART may have benefits even when there is not immune recovery,^{3,22} we sought to evaluate the outcomes of treatments in the HAART era, using the prospective observational study, the Longitudinal Study of the Ocular Complications of AIDS (LSOCA), a cohort study conducted entirely in the HAART era.

Patients and Methods

Patients and follow-up

The LSOCA cohort enrolled patients with AIDS according to the 1993 Centers for Disease Control and Prevention revised surveillance case definition of AIDS.^{11,23} Patients were enrolled with and without ocular opportunistic infections, but the cohort was enriched for patients with ocular opportunistic infections, particularly CMV retinitis.¹¹ Cytomegalovirus retinitis was diagnosed by SOCA-certified ophthalmologists based on the characteristic clinical picture of a full-thickness necrotizing retinitis. Patients with CMV retinitis were enrolled regardless of immune recovery status and duration of the retinitis. Because anti-CMV treatment typically is discontinued for sustained immune recovery to a CD4+ T cell count ≥ 100 cells/ μ L¹⁷ and does not affect the outcomes of patients with immune recovery,¹⁸ we evaluated the outcomes of patients enrolled with CMV retinitis with CD4+ T cells <100 cells/ μ L at enrollment and those with incident CMV retinitis during follow-up.⁷ Follow-up for treatment outcomes continued until the participant had discontinued anti-CMV treatment, death, or end of the study period, 31 December 2011.

Patients with CMV retinitis were seen for data collection every 3 months, at which time a history and complete eye examination were performed. Standard fundus photographs were taken and sent to a reading center, where graders, masked as to treatment, evaluated the photographs for retinitis progression extent of retinal involvement by CMV retinitis, and location of the retinitis, as previously described.^{11,24} For analysis purposes, a binary classification of location was used – whether zone 1 was involved or not, as zone 1 involvement is thought to be immediately vision threatening. Zone 1 encompasses the region around the optic nerve and the macula and is defined as the retina within one disc diameter of the optic nerve or two disc diameters of the center of the fovea.²⁵ Cytomegalovirus lesions also were classified as having active borders (“active lesions”) or inactive borders. Features of active lesions includes edematous and opaque borders with satellite lesions, whereas inactive lesions had an atrophic appearance with sharp borders without edema.²⁵ Institutional Review Board (IRB) approval was obtained from the IRB’s of each clinical center and the three resource centers (see Supplemental Material for names of these institutions). Informed consent was obtained from all patients prior to enrollment into LSOCA. The study was conducted in accordance with the Declaration of Helsinki and HIPAA regulations.

Outcomes

Retinitis progression was determined from the photograph grading and was defined as movement of a border of a CMV lesion $> \frac{1}{2}$ disc diameter along a front $> \frac{1}{2}$ disc diameter is size or the occurrence of a new lesion $\frac{1}{4}$ disc area in size.^{2,25} Visual acuity was measured using logarithmic acuity “ETDRS” eye charts and recorded as the number of letters read.^{11,24,27} Event rates for visual acuity falling below thresholds were determined: worse than 20/40 (visual impairment) and 20/200 or worse (blindness). Visual fields were measured using the SOCA-modified quantitative “DRS” visual fields on the Goldmann perimeter, which produce a visual field score.²⁸ The normal field score is $\sim 800^\circ$ and the lower limit of normal is $\sim 700^\circ$. Event rates for the field being reduced below thresholds of 600° (loss of $\sim 25\%$ of normal field) and 400° (loss of $\sim 50\%$ of normal field) were determined. Data on second eye disease were determined from the clinical examination and on visceral disease from the history and medical record review.^{2,11,29}

Analyses and statistics

For comparison of enrollment characteristics of patients, patients were classified based on the treatment being received at enrollment or if treatment was initiated upon enrollment (or

after diagnosis for incident cases) based on the initial treatment given. For outcome analyses, patients or eyes were classified based on the question being addressed. For the evaluation of the impact of systemic treatment on systemic outcomes, patients were classified as receiving systemic treatment or not (i.e. intraocular therapy only). Hence patients in the systemic treatment group could have received ganciclovir implants or intravitreal injections in addition to systemic therapy but had to receive systemic therapy. For the analysis of ocular outcomes, eyes were grouped as being treated with systemic treatment only, ganciclovir implants (with or without systemic therapy) and intravitreal injections. Previous work from the pre-HAART era demonstrated that implants with or without systemic therapy were more similar to each other than to systemic therapy only in terms of retinitis progression (although there were small differences favoring the combination of implant and systemic), as the implant provides much higher levels of ganciclovir in the eye than does systemic therapy.^{20,21,30} An analysis of the different intravitreal injection groups in this study (e.g. with or without an implant) suggested that they behaved similarly to each other but differently than the systemic only group and the implant without injections group (data not shown) and, therefore, were grouped together for analysis purposes.

Cytomegalovirus retinitis treatment information was obtained from study forms completed at enrollment and follow-up visits. All visits from treatment initiation to treatment cessation were included for analysis. Missing treatment data (<11%) for any interim visit were imputed by using the last-observation-carried-forward technique. Systemic treatment was indicated if present at the current visit, injection if given within the last 28 days, and implant if implanted within the last nine months. Patient outcomes were assessed as a time-fixed effect of treatment regimen as only 13.2% of patients switched between systemic and non-systemic therapies. Ocular outcomes used treatment as a time-varying covariate as 44.8% of patients switched once or more among the three groups (systemic, implant, injection).

Characteristics at enrollment or the time of diagnosis of CMV retinitis were compared among treatment groups using the chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.³¹ Nominal P-values were used for subgroup differences without adjustment for multiple comparisons or multiple outcomes. Person time was calculated from the first visit where CMV retinitis treatment was initiated to the first occurrence of the outcome of interest or censoring at the last visit where treatment was administered. Rates were calculated as number of events per 100 person-years (PY) for patient-related outcomes and per 100 eye-years (EY) for ocular outcomes. Cox proportional hazard regression without (crude) and with (adjusted) adjustment for CD4+ T cells, HIV load, and HAART use were used to assess the magnitude and significance of the association between patient outcomes and treatment regimen.³² To obtain the relative risks for ocular outcomes, unadjusted and adjusted Cox regression models utilizing robust variance estimation were constructed;³³ this approach accounts for the correlation between eyes. The adjusted models controlled for CD4+ T cells, HIV load, HAART use, duration of CMV retinitis, zone 1 involvement, CMV lesion activity, and area of CMV retinitis. Statistical analyses were performed using SAS/STAT (software, version 9.2. Copyright 2002–2008. SAS Institute, Inc. Cary, NC, USA) and Stata Corp. (2011 Stata Statistical Software Release 12. StataCorp LP. College Station, TX, USA).

Results

Patients

505 patients with CMV retinitis were enrolled in LSOCA, and an additional 29 patients developed CMV retinitis during follow-up. Of these 534 patients 224 were enrolled with a CD4+ T cell count < 100 cells/ μ L and were treated, and 26 incident cases during follow-up

were treated for a total of 250 patients in the data set. Of these 250 participants, 35.2% had bilateral disease at enrollment into LSOCA or at the diagnosis of CMV retinitis for a total of 338 eyes with CMV retinitis. Mean follow-up of the study population was 5.0 years with a median of 4.3 years and an interquartile range of 1.7 to 7.5 years. Total follow-up time for the study population was 375 PY; follow-up did not differ significantly by treatment regimen.

Characteristics of the study participants are listed in Table 1 (available at <http://aaojournal.org>). In general the patients in the different treatment regimens had similar demographic characteristics (age, gender, HIV-infection risk group), and immunologic profiles (enrollment CD4+ T cells, nadir CD4+ T cells, enrollment HIV load). However, patients receiving implants and systemic therapy appeared to have a longer duration of CMV retinitis before enrollment (median 6.0 months), whereas those receiving intravitreal injections appeared to have a shorter duration of CMV retinitis at enrollment (median 0.4 months). In the total cohort studied, about 70% were receiving HAART at enrollment and 41% experienced immune recovery to a CD4+ T cell count ≥ 100 cells/ μ L. The use of HAART at enrollment and the percent achieving immune recovery were not significantly different among the different treatment groups.

In general, the severity of eye disease appeared similar among the different groups with respect to retinal area involved and Goldmann visual field score (Table 1, available at <http://aaojournal.org>). Overall about one-half of eyes had a CMV lesion affecting 10–25% of the retina in size and slightly over one-fourth had a lesion affecting over 25% of the retina. The median visual field size (quantitative Goldmann visual field score = 582° of field) represented a loss of visual field of approximately 25% of the visual field (loss of ~25% of field equals a quantitative Goldmann visual field score 600° of field). Enrollment visual acuities generally were good with ~72% of involved eyes having enrollment acuity of 20/40 or better, and only 12.4% of eyes having a visual acuity of 20/200 or worse. There were no significant differences in the distributions of good visual acuity ($P = 0.15$) or blindness ($P = 0.51$) among the different treatment groups. Overall nearly 40% of eyes had zone 1 involvement. However, the eyes treated with intravitreal injections appeared to have a greater proportion of zone 1 involvement (69%, $P = 0.002$) and active lesions (81%, $P < 0.01$) than did the other groups.

Oral ganciclovir vs. valganciclovir

Approximately 30% of patients treated with oral anti-CMV therapy received oral ganciclovir (as opposed to valganciclovir). Results were not significantly different for the two groups. Adjusted hazard ratios (HR) for valganciclovir vs. oral ganciclovir were: for mortality 0.6 (95% CI 0.3, 1.1, $P = 0.14$); for visceral CMV 0.5 (95% CI 0.04, 6.4, $P = 0.61$); and for CMV retinitis progression 0.9 (95% CI 0.3, 2.7, $P = 0.97$). Therefore, the two groups were combined for all subsequent analyses comparing systemic therapy to intraocular therapy.

Systemic outcomes

Systemic outcomes are presented as Table 2. Regimens including systemic anti-CMV therapy were associated with a 50% reduction in mortality (adjusted HR = 0.5, $P = 0.006$). This mortality difference was present despite similar rates of immune recovery between regimens without and with systemic anti-CMV therapy, which were 41.0/100 PY vs. 41.8/100 PY, respectively (adjusted HR for immune recovery for systemic anti-CMV therapy vs. none = 1.1, $P = 0.61$). The use of HAART at baseline or during follow-up was similar between the two groups; for patients with intraocular only anti-CMV therapy, 79% were treated with HAART at enrollment or during follow-up vs. 91% of those treated with a systemic anti-CMV therapy containing regimen ($P = 0.20$). Dissemination of CMV disease to

the second eye in patients with unilateral disease and to the viscera was greater with regimens that contained only intraocular treatments than those that contained systemic anti-CMV agents. There was an 80% reduction in the rate of second eye disease with regimens containing a systemic anti-CMV agent (rate = 10.9/100 PY, adjusted HR = 0.2, P=0.0005) vs. regimens with only intraocular therapy (rate = 54.6/100 PY), and a 90% reduction in the incidence of visceral CMV disease with regimens containing a systemic anti-CMV agent (rate = 3.7/100 PY, adjusted HR = 0.1, P=0.004) vs. those without a systemic anti-CMV agent (rate 24.1/100 PY). The enrollment frequencies of visceral CMV were not statistically different between the two groups: 14.7% for those treated with systemic anti-CMV therapy vs. 6.1% for those treated with only intraocular therapy (P=0.27). A sensitivity analysis was performed in which follow-up was censored after the CD4+ T cells rose to 100 cells/ μ L for 6 months (the recommended threshold for discontinuing anti-CMV treatment^{17,18}); the difference in follow-up time was minimal (2.6% less), and the results of these analyses were both qualitatively and quantitatively similar (data not shown).

Ocular outcomes

Ocular outcomes are presented as Table 3 and visual outcomes as Table 4. In general, patients treated with intravitreal injections did worse than patients treated with other regimens, whereas patients treated with systemic treatment only and those treated with ganciclovir implants tended to behave more similarly. The rates of retinitis progression were: systemic treatment only 16.5/EY; implant 22.3/EY (adjusted HR= 0.5, P=0.26); and intravitreal injections 96.1/EY (adjusted HR=3.4, P=0.004). Severe visual field loss results (to <400° total field) tended to parallel progression results. The rates of visual field loss to <400° of field were: systemic treatment only 11.9/EY; implants 10.8/EY (adjusted HR=0.5, P=0.45); and intravitreal injections 76.2/EY (adjusted HR=5.5, P<0.01). Although the crude analysis suggested that the rates of visual field loss to <600° field also were greater in the injection group, the adjusted analysis did not reveal any significant difference. The rates of loss of visual field to <600° of field were: systemic treatment only 31.7/EY; implants 29.7/EY (adjusted HR=0.8, P=0.75); and intravitreal injections 96.2/EY (crude HR=2.8, P=0.046; adjusted HR=1.1, P=0.73).

Visual acuity outcomes also suggested that patients treated with intravitreal injections did worse in both the crude and adjusted analyses. The rates of loss of visual acuity to worse than 20/40 were: systemic treatment only 18.1/100 EY; ganciclovir implants 32.8/100 EY (adjusted HR=1.6, P=0.35); and injection therapy 84.6/100 EY (adjusted HR=4.7, P<0.01). The rates of visual acuity loss to 20/200 or worse were: systemic therapy only 6.2/100 EY; ganciclovir implants 12.5/100 EY (adjusted HR=0.7, P=0.68); and injection therapy 43.2/100 EY (adjusted HR=5.2, P=0.002).

Treatment side effects

Approximately 90% of those patients receiving systemic anti-CMV therapy received systemic ganciclovir. The enrollment frequencies of systemic side effects associated with anti-CMV treatment were not significantly different between those receiving systemic therapy and those receiving only intraocular therapy. The enrollment frequencies of patients receiving systemic anti-CMV therapy vs. those receiving only intraocular therapy, respectively were: neutropenia to an absolute neutrophil count < 750 cells/ μ L, 6.9% vs. 6.1% (P>0.99); anemia to a hemoglobin < 8.5 gm/dL, 4.1% vs. 3.0% (P>0.99); thrombocytopenia to a platelet count <50,000/ μ L, 0.5% vs. 3.0% (P=0.24); and an elevated creatinine >1.5 mg/dL 6.9% vs. 9.1% (P=0.71). The rates of hematologic toxicities were not substantially or significantly greater among those receiving systemic anti-CMV therapies than among those receiving only intraocular therapy (Table 5). The rates of neutropenia to a level < 750 cells/ μ L were 21.0/100 PY for those receiving intraocular therapy only vs.

18.7/100 PY for those receiving systemic anti-CMV therapy (HR = 0.9, P = 0.96). The rates of anemia to a hemoglobin <8.5 gm/dL were 29.4/100 PY for those receiving intraocular therapy only vs. 16.6/100 PY for those receiving systemic anti-CMV therapy (HR = 0.7, P = 0.45). The rates of thrombocytopenia to a platelet count <50,000/ μ L were 25.3/100 PY for those receiving intraocular therapy only vs. 7.1/100 PY for those receiving systemic therapy (HR = 0.3, P=0.02). Rates of nephrotoxicity were similar between the two groups. The rates of a serum creatinine >1.5 mg/dL were 20.0/100 PY for those treated with intraocular therapy only vs. 16.3/100 PY for those treated with systemic anti-CMV therapy (HR = 0.8, P=0.58).

There was one case of endophthalmitis after an intravitreal injection and two cases after ganciclovir implant surgery. The rates of endophthalmitis were: after an intravitreal injection, 0.012 per injection (0.017/EY, 95% CI 0.006, 0.05) and after a ganciclovir implant, 0.016 per implant (0.01/EY, 95% CI 0.002, 0.04).

Discussion

Our results suggest that, in the HAART era, the use of systemic anti-CMV medications for patients with CMV retinitis has benefits in terms of reduced mortality, reduced visceral CMV disease, and, among those with unilateral disease, reduced dissemination to the second eye. These benefits were identified in the pre-HAART era,^{3,20–22} but whether they persisted in the face of HAART was unknown, as HAART may have benefits even when there is not immune recovery to a level sufficient for discontinuing anti-CMV therapy.^{3,22} These benefits appeared to accrue from systemic anti-CMV treatment and not be due to evident confounding. The groups treated with and without systemic anti-CMV treatments had similar presentation immunologic defects in terms of presentation and nadir CD4+ T cells, HIV loads, and HAART use. The use of HAART at enrollment or during follow-up was not significantly different between the two groups, and the rates of immune recovery also were similar. The adjusted hazard ratios and significance, which adjusted for CD4+ T cells, HIV load, and HAART use, were not substantially different from the crude analyses. As such the difference between the two groups appears to be due to the use of systemic anti-CMV drugs. Furthermore, the decreased mortality outcome with systemic therapy also was seen in the pre-HAART era,²² suggesting that systemic anti-CMV therapy has a benefit on survival as long as there is immune compromise to a CD4+ T cell level <100 cells/ μ L.

The survival benefit from systemic anti-CMV therapy is consistent with the known pathogenetic interactions between CMV and HIV. In patients with AIDS and CMV retinitis, CMV is a systemic infection, as evidenced by the ability to isolate CMV from the blood using viral culture technology in 80% of patients at the time of diagnosis of the retinitis and identify CMV DNA in the blood of 60% of patients using PCR amplification.^{34,35} CMV and HIV trans-activate each other, and CMV has additive immunosuppressive effects to HIV.³ Patients with AIDS and CMV retinitis have a 60% greater mortality than those without, even after adjustment for immunologic, HIV virologic, and treatment factors.³⁶ As such inhibition of CMV replication would be expected to decrease these interactions, decrease the immune compromise (i.e. improve immune function), and improve survival, a result seen in the pre-HAART era.^{3,22} The results of our study have implications for treatment, in that they suggest that, when possible, patients with newly-diagnosed CMV retinitis should be treated with systemic anti-CMV agents (whether or not concomitant intravitreal therapy is given), at least until there is sustained immune recovery (CD4+ T cells 100 cells/ μ L for 6 months),³ at which level it appears that the benefits of immune recovery make the use of systemic anti-CMV treatment unnecessary in most cases.¹⁸

The analyses of ocular outcomes appear to suggest that treatment regimens containing intravitreal injections may do worse than those containing systemic therapy or ganciclovir implants. This result was consistent for both retinitis progression and severe loss of visual field (to $<400^\circ$ field), both of which are measures of control of retinitis. Visual field loss to $<600^\circ$ of field was significantly worse for intravitreal injection therapy in the crude analysis but not in the adjusted one. The difference between the crude and adjusted analyses may be due in part to the slight imbalances in enrollment visual field size, area of CMV retinitis, and lesion activity.

Again, because LSOCA is a cohort study and not a clinical trial, one question in interpreting these results is whether there were differences other than treatment regimen among these groups that could account for these observed differences (confounders). The intravitreal injection group contained a few eyes with implants (old) which were also receiving injections, and these eyes might be expected to do worse (due to presumed resistant CMV). Intravitreal injections (particularly of foscarnet) sometimes are used in patients with ganciclovir-resistant CMV, and patients with resistant CMV typically do worse than patients with sensitive CMV.^{37,38} However, resistant CMV is associated with longer duration of anti-CMV therapy^{39–41} and patients in the injections group had a shorter duration of retinitis at enrollment than those in the systemic only and implant groups, so they would be expected to be less likely to have resistant CMV. No CMV resistance testing was performed as part of this study. Furthermore, these eyes behaved like those receiving injections without the any other therapy. Similarly, eyes receiving injections were more likely to have active retinitis and conceivably might be more likely to progress before the treatment had its effect. However, previous data have shown an accelerating pace of CMV retinitis progression over time among patients with immune compromise,⁴² and patients treated with injections had a shorter duration of CMV retinitis; therefore, those eyes given injections again might be expected to respond better to a treatment regimen. Furthermore, there were no significant differences in enrollment immune function (CD4+ T cell count, nadir CD4+ T cell count, HIV load), HAART use, and immune recovery among those treated with these different regimens, and the extent of retinitis at enrollment (percent of retina involved) also was not significantly different among eyes treated with these different regimens. Finally, adjustment for these factors and for the activity of the retinitis did not alter the result that those treated with injections appeared to do worse.

Results that possibly could be confounded are the visual acuity outcomes. Zone 1 involvement was more common among those treated with injections than among those treated with other regimens (69% vs. 34–39%). Since damage to the fovea or optic nerve is the leading cause of vision loss in eyes with CMV retinitis, eyes with zone 1 involvement might be expected to suffer greater rates of visual impairment and blindness.^{43,44} Intravitreal injections might have been used in eyes at risk of immediate visual loss because of the location of the CMV lesion in the belief that higher drug levels in the eye from injections would reduce the likelihood of visual loss, (a treatment by indication bias). As such any suggestion of an apparent inferiority of intravitreal injections probably should not be based solely on visual acuity outcomes. However, adjustment for CD4+ T cells, HIV load, HAART use, duration of CMV retinitis, CMV lesion size, CMV lesion activity, and CMV lesion location did not alter the conclusion that patients in LSOCA treated with injections appeared to do worse in terms of visual acuity outcomes. Moreover, the retinitis progression and severe visual field loss, as well as the adjusted visual acuity outcomes, all suggest that intravitreal injections did not do as well as systemic therapy or implant therapy for controlling the retinitis.

Nevertheless, caution still should be exercised in interpreting these results, particularly as regards any unknown bias between treatments that may have influenced the results.

Although adjustments for known factors affecting these outcomes did not qualitatively alter the interpretation of most of the results, there may have been unrecognized factors for which we did not adjust. Furthermore, the sample size was small, and the absence of any evident differences in ocular outcomes between the systemic only group and the implant group may be a type II error. The numbers of patients treated with intravitreal injection therapy and with implant therapy were small limiting the power to analyze the results of these treatments, resulting in wide confidence intervals, and precluding subgroup analyses. Randomized clinical trials from the pre-HAART era demonstrated longer times to CMV retinitis progression among those given ganciclovir implant therapy compared to those given systemic ganciclovir only,^{20,21} and the adjusted hazard ratios in our study for progression and severe visual field loss are both 0.5 for the implant vs. systemic therapy only, but lack statistical significance. In that regard, it should be noted that the observed rates were greater for the implants than for systemic therapy only, but that adjustment for potential confounders resulted in a quantitatively different hazard ratio, emphasizing the potential role of confounders. As such, one cannot conclude that systemic therapy is similar to implant therapy for control of CMV retinitis in the HAART era just because of the lack of statistical “significance”. It also is conceivable that implants remain better at controlling the retinitis, and the lack of statistical significance may simply be due to treatment by indication bias and/or small sample size. Nevertheless, the magnitude of the differences observed was such that significant differences were detected between intraocular therapy only (implants or injections) and systemic anti-CMV therapy for systemic outcomes, and the results suggesting benefit from systemic therapy on systemic outcomes are consistent with those seen in clinical trials of ganciclovir implants.^{20,21} The consistency of these findings suggests that the observed differences in the systemic outcomes are due to the treatment regimens.

The use of repetitive intravitreal injections without systemic ganciclovir (or implants) for the treatment of CMV retinitis in resource-poor countries has been advocated as an affordable method to control the disease.⁴⁵ Although this approach may be the best approach available in these areas, our data suggest that this approach is less appropriate when systemic ganciclovir is available and affordable, as systemic therapy improves survival and decreases dissemination. Furthermore, our data suggest that intravitreal injections solely as anti-CMV therapy may be less effective for controlling the retinitis, although as noted above, we cannot exclude fully the possibility that these differences are due to residual confounding. Nevertheless it is unlikely that intravitreal injections alone are superior to systemic therapy for controlling the retinitis and may be worse. In addition, because of the small sample size, our data could not be used to adequately evaluate any potential benefits of adding intravitreal injections to systemic therapy.

In conclusion, in the era of HAART, for those patients with immune compromise, systemic anti-CMV therapy appears to have benefits on systemic outcomes, including mortality and dissemination of CMV, and within the limitations of this study, intravitreal injection therapy appeared to do worse than systemic therapy or ganciclovir implants for ocular outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 2

Comparison of Patient Outcomes for Patients with Cytomegalovirus Retinitis and AIDS by Cytomegalovirus Treatment Regimen

Outcome	Overall	Intraocular therapy only*	Systemic therapy*
<i>Mortality</i>			
Patients at risk	250	33	217
Number of events	170	27	143
Person-years of follow-up	480.7	39.2	441.5
Rate (/100 person-years)	35.3	68.8	32.3
Hazard ratio (95% CI)		1.0	0.5 (0.3, 0.7)
P-value		-	0.001
Adjusted hazard ratio (95% CI) [†]		1.0	0.5 (0.3, 0.8)
P-value		-	0.006
<i>2nd eye involvement</i>			
Patients at risk	162	24	138
Number of events	33	10	23
Person-years of follow-up	227.5	18.3	209.1
Rate (/100 person-years)	14.5	54.6	10.9
Hazard ratio (95% CI)		1.0	0.2 (0.1, 0.5)
P-value		-	0.0002
Adjusted hazard ratio (95% CI) [†]		1.0	0.2 (0.1, 0.5)
P-value		-	0.0005
<i>Visceral CMV[‡] disease</i>			
Patients at risk	215	31	184
Number of events	17	5	12
Person-years of follow-up	338.6	20.7	317.8
Rate (/100 person-years)	5.0	24.1	3.7
Hazard ratio (95% CI)		1.0	0.1 (0.04, 0.4)
P-value		-	0.0008
Adjusted hazard ratio (95% CI) [†]		1.0	0.1 (0.05, 0.5)
P-value		-	0.004

* Systemic therapy includes all regimens in which systemic treatment was given, regardless of any intraocular therapy. Intraocular therapy only includes ganciclovir implants and intravitreal injections without any concomitant systemic therapy.

[†] Adjusted hazard ratios, 95% confidence intervals (CI), and P-values obtained from Cox proportional regression model controlling for CD4+ T cells, human immunodeficiency virus (HIV) load, and highly active antiretroviral therapy (HAART) use.

[‡] CMV = cytomegalovirus.

Table 3

Comparison of Ocular Outcomes of Cytomegalovirus Retinitis Treatments

Outcome	Overall Population	Systemic Treatment only	Ganciclovir Implant [*]	Intravitreal Injections [†]
<i>Retinitis progression</i>				
Eyes at risk	306	209	57	40
Number of events	67	51	4	12
Eye-years of follow-up	339.4	309.1	17.9	12.5
Rate (/100 eye-years)	19.7	16.5	22.3	96.1
Hazard ratio vs systemic only	-	1.0	1.2	7.1
95% confidence interval	-	-	0.4, 3.3	3.7, 13.5
P-value	-	-	0.68	<0.01
Adjusted hazard ratio [‡]		1.0	0.5	3.4
95% confidence interval		-	0.2, 1.5	1.4, 8.1
P-value		-	0.26	0.004
<i>Retinal detachment</i>				
Eyes at risk	307	219	51	37
Number of events	30	21	4	5
Eye-years of follow-up	417.5	381.3	21.8	14.4
Rate (/100 eye-years)	7.2	5.5	18.3	34.8
Hazard ratio vs systemic only	-	1.0	2.6	5.5
95% confidence interval	-	-	0.8, 8.3	2.2, 13.4
P-value	-	-	0.08	<0.01
Adjusted hazard ratio [‡]		1.0	1.8	3.7
95% confidence interval		-	0.5, 6.2	1.2, 11.0
P-value		-	0.30	0.01
<i>Immune recovery uveitis</i>				
Eyes at risk	328	226	61	41
Number of events	24	18	4	2
Eye-years of follow-up	491.3	440.8	31.6	18.9
Rate (/100 eye-years)	4.9	4.1	12.6	10.6
Hazard ratio vs systemic only	-	1.0	5.0	2.1
95% confidence interval	-	-	1.6, 15.2	0.4, 11.1
P-value	-	-	0.005	0.36
Adjusted hazard ratio [‡]		1.0	11.2	2.8
95% confidence interval		-	3.2, 39.0	0.6, 12.2
P-value		-	<0.01	0.15

^{*}Ganciclovir implant with or without systemic therapy.

[†]Intravitreal injections with or without systemic therapy and with or without implants.

[‡]Adjusted hazard ratios, 95% confidence intervals, and P-values obtained from Cox proportional hazard regression model controlling for CD4+ T cells, human immunodeficiency virus (HIV) load, highly active antiretroviral therapy (HAART) use, duration of cytomegalovirus (CMV) retinitis, zone 1 involvement, CMV border activity, and area of CMV retinitis.

Table 4

Comparison of Visual Outcomes of Cytomegalovirus Retinitis Treatments

Outcome	Overall Population	Systemic Treatment only	Ganciclovir Implant [*]	Intravitreal Injections [†]
<i>Visual field loss</i>				
<i>To <600° (~25% loss of field)</i>				
Eyes at risk	136	100	24	12
Number of events	41	33	3	5
Eye-years of follow-up	119.4	104.2	10.1	5.2
Rate (/100 eye-years)	34.3	31.7	29.7	96.2
Hazard ratio vs systemic only	-	1.0	1.0	2.8
95% confidence interval	-	-	0.3, 3.1	1.0, 7.8
P-value	-	-	1.00	0.046
Adjusted hazard ratio [‡]		1.0	0.8	1.1
95% confidence interval		-	0.2, 3.1	0.4, 3.3
P-value		-	0.75	0.73
<i>To <400° (~50% loss of field)</i>				
Eyes at risk	230	163	44	23
Number of events	36	26	2	8
Eye-years of follow-up	247.3	218.3	18.5	10.5
Rate (/100 eye-years)	14.6	11.9	10.8	76.2
Hazard ratio vs systemic only	-	1.0	0.8	8.2
95% confidence interval	-	-	0.2, 3.0	3.6, 18.8
P-value	-	-	0.81	<0.01
Adjusted hazard ratio [‡]		1.0	0.5	5.5
95% confidence interval		-	0.1, 2.3	2.1, 14.4
P-value		-	0.45	<0.01
<i>Visual acuity loss</i>				
<i>To worse than 20/40</i>				
Eyes at risk	237	172	43	22
Number of events	58	41	6	11
Eye-years of follow-up	257.5	226.2	18.3	13.0
Rate (/100 eye-years)	22.5	18.1	32.8	84.6
Hazard ratio vs systemic only		1.0	1.6	5.2
95% confidence interval		-	0.6, 4.0	2.7, 10.0
P-value		-	0.25	<0.01
Adjusted hazard ratio [‡]		1.0	1.6	4.7
95% confidence interval		-	0.5, 4.8	2.0, 10.9
P-value		-	0.35	<0.01
<i>To 20/200 or worse</i>				
Eyes at risk	286	203	51	32
Number of events	29	19	3	7

Outcome	Overall Population	Systemic Treatment only	Ganciclovir Implant*	Intravitreal Injections†
Eye-years of follow-up	348.6	308.3	24.0	16.2
Rate (/100 eye-years)	8.3	6.2	12.5	43.2
Hazard ratio vs systemic only		1.0	1.8	6.2
95% confidence interval		-	0.5, 6.3	2.5, 15.4
P-value		1.0	0.33	<0.01
Adjusted hazard ratio‡		-	0.7	5.2
95% confidence interval		-	0.1, 3.2	1.8, 14.8
P-value			0.68	0.002

* Ganciclovir implant with or without systemic therapy.

† Intravitreal injections with or without systemic therapy and with or without implants.

‡ Adjusted hazard ratios, 95% confidence intervals, and P-values obtained from Cox proportional hazard regression model controlling for CD4+ T cells, human immunodeficiency virus (HIV) load, highly active antiretroviral therapy (HAART) use, duration of cytomegalovirus (CMV) retinitis, zone 1 involvement, CMV border activity, and area of CMV retinitis.

Table 5

Comparison of Laboratory Results for Patients with Cytomegalovirus Retinitis and AIDS by Cytomegalovirus Treatment Regimen

Outcome	Overall	Intraocular therapy only*	Systemic therapy*
<i>ANC[§] <750 cells/μL</i>			
Patients at risk	226	31	195
Number of events	57	5	52
Person-years of follow-up	300.9	23.7	277.2
Rate (/100 person-years)	18.9	21.0	18.7
Hazard ratio (95% CI)		1.0	0.9 (0.3, 2.4)
P-value		-	0.96
Adjusted hazard ratio (95% CI) [†]		1.0	1.0 (0.3, 2.9)
P-value		-	0.95
<i>Hemoglobin < 8.5 gm/dL</i>			
Patients at risk	237	32	205
Number of events	58	6	52
Person-years of follow-up	333.0	20.4	312.6
Rate (/100 person-years)	17.4	29.4	16.6
Hazard ratio (95% CI)		1.0	0.7 (0.3, 1.6)
P-value		-	0.45
Adjusted hazard ratio (95% CI) [†]		1.0	0.9 (0.3, 2.3)
P-value		-	0.83
<i>Platelets <50,000/μL</i>			
Patients at risk	244	32	212
Number of events	30	5	25
Person-years of follow-up	369.9	19.7	350.1
Rate (/100 person-years)	8.1	25.3	7.1
Hazard ratio (95% CI)		1.0	0.3 (0.1, 0.8)
P-value		-	0.02
Adjusted hazard ratio (95% CI) [†]		1.0	0.2 (0.1, 0.8)
P-value		-	0.01
<i>Serum creatinine >1.5mg/dL</i>			
Patients at risk	223	29	194
Number of events	60	8	52
Person-years of follow-up	358.4	39.9	318.4
Rate (/100 person-years)	16.7	20.0	16.3
Hazard ratio (95% CI)		1.0	0.8 (0.3, 1.7)
P-value			0.58
Adjusted hazard ratio (95% CI) [†]		1.0	0.8 (0.3, 2.0)
P-value			0.70

* Systemic therapy includes all regimens in which systemic treatment was given, regardless of any intraocular therapy. Intraocular therapy only includes ganciclovir implants and intravitreal injections without any concomitant systemic therapy.

[†] Adjusted hazard ratios, 95% confidence intervals (CI), and P-values obtained from Cox proportional regression model controlling for CD4+ T cells, human immunodeficiency virus (HIV) load, and highly active antiretroviral therapy (HAART) use.

[‡] CMV = cytomegalovirus.

[§] ANC = absolute neutrophil count.